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Noticeable Hyperbilirubinemia Following Major Hepatectomy in Patients with Biliary Tract Carcinoma

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Abstract

Serum bilirubin concentrations were examined in patients who received hepatectomy for biliary tract carcinoma. They were divided into two groups according to the presence or absence of preoperative obstructive jaundice (POJ): the POJ group (n=14) and non-POJ group (n=10). The POJ group underwent percutaneous transhepatic drainage to delineate jaundice before definitive surgery. Total bilirubin concentration in the POJ group had increased at 1, 3, 5, 7 and 14 days after operation compared to the non-POJ group; the direct bilirubin level had increased at 1, 3, 5 and 7 days, and the indirect bilirubin level had increased at 1 and 3 days. Liver functional data before and 14 days after the operation were similar for the two groups. The incidence of cholangitis was higher in the POJ group than in the non-POJ group. Blood loss was greater in the POJ group than in the non-POJ group. The morbidity rate in the POJ group was higher than that in the non-POJ group.

These results suggest that characteristic hyperbilirubinemia developed after major hepatectomy in patients with biliary tract carcinoma, and the bilirubin response is evoked by underlying preoperative biliary passing disturbance.

Introduction

Hyperbilirubinemia after a general operation has been considered under three basic pathophysiologic mechanisms: increased pigment load from overproduction of bilirubin, impaired excretion of bilirubin due to hepatocellular damage, and obstruction of the extrahepatic bile ducts[1]. Hepatic lobectomy also produces a transient increase in the serum bilirubin concentration[2-5] and the increased bilirubin concentration is induced by critical hepatic factors, such as severe reduction of the liver cell mass, underlying liver disease, and acute insufficiency of cells in the residual liver[5-8]. Deviations in the serum bilirubin concentration from the normal pattern have therefore been regarded as an early sign of liver insufficiency after hepatectomy; the increase in the bilirubin concentration after major hepatectomy is an indicator highly sensitive to liver dysfunction and is correlated positively with morbidity and mortality[6,7,9]. Radical surgery with major hepatectomy has been attempted for advanced biliary tract carcinoma[10-15]. Biliary tract carcinoma often accompanies biliary obstruction, which is believed to impair hepatic function, and in this situation liver failure fol-

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lowed by hepatectomy can lead to serious complications. However, the relation of postoperative hyperbilirubinemia to preoperative biliary passage disturbance has not been examined in patients with biliary tract carcinoma.

Recently we have observed preoperative biliary passing disturbance that resulted in a further increase in the serum bilirubin concentration in patients who received hepatectomy for biliary tract carcinoma.

Subjects and Methods

A total of 24 patients underwent major hepatectomy for biliary tract carcinoma. A patient who underwent either concomitant pancreatoduodenectomy or plasma exchange was excluded. They were classified into two groups according to the presence or absence of preoperative obstructive jaundice (POJ), i.e. the POJ group (n=14) and non-POJ group (n=10). Details of these cases are shown in Table 1.

Patients with POJ underwent percutaneous transhepatic drainage to delineate jaundice before definitive surgery[16]. The site of the bile duct obstruction and the extent of the disease were deter-

Table 1 Clinical data for the non-POJ (I, n=10) and POJ (II, n=14) groups

	I	II
Sex		
Male	5	6
Female	5	8
Age (year)	66±3	59±3
Diagnosis		
Gallbladder carcinoma	5	5
Extrahepatic bile duct carcinoma	2	7
Intrahepatic bile duct carcinoma	4	2

Values are the means±SEM.

Table 2 Intraoperative conditions in the non-POJ (I, n=10) and POJ (II, n=14) groups

	I	II
Hepatectomy type		
Left trisegmentectomy	1	1
Extended right lobectomy	2	8
Right lobectomy	0	2
Extended left lobectomy	4	0
Left lobectomy	2	3
Anterior and medial segmentectomy	1	0
Resected liver weight/body weight (g/kg)	8.1±1.2	13.0±1.7
Operation time (min)	532±50	597±20
Intraoperative bleeding (g)	1107±168[a]	2659±555
Intraoperative blood transfusion (ml)	694±187	1214±335

Values are the means±SEM. [a] $p<0.05$ vs II.

mined by the preparatory procedure[17,18]. Patients after drainage received bile refeeding to return the bile to the enterohepatic circulation similarly to internal biliary drainage[19]. The operations were performed after lowering the serum bilirubin concentration to less than 3.0 mg/dl. The major hepatectomy with bile duct resection and en bloc lymphonode dissection of the hepatoduodenal ligament were conducted. The biliary tract was reconstructed by anastomosis of the jejunum to intrahepatic bile ducts in a type of Roux-en Y. Operative modes and conditions are summarized in Table 2.

Liver functional parameters estimated are as follows: GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; LDH, lactic dehydrogenase; Alp, alkaline phosphatase; γGTP, γ-glutamyl transpeptidase; ChE, cholinesterase; T.Bil, total bilirubin; D.Bil, direct bilirubin; I.Bil, indirect bilirubin; Alb, albumin; PT, prothrombin time; HPT, hepaplastin test; OGTT, oral glucose tolerance test; KICG, indocyanine green disappearance rate. These parameters were combined as required. Liver functional parameters were estimated before and 1, 3, 5, 7, 10 and 14 days after the operation. Preoperative cholangitis was also looked for.

In the POJ group, fresh frozen plasma was used to substitute circulating plasma volume as required.

Pathological observations were compared by Fisher's exact test. The data were ANOVA analyzed, and specific values were evaluated by Duncan's multiple range test. *t*-test was also applied when necessary.

Results

No significant difference between the two groups was seen in the T.Bil, D.Bil and I.Bil concentrations before the operation (Figs. 1 and 2). The T.Bil concentration in the POJ group had increased significantly at 1, 3, 5, 7 and 14 days after the operation when compared to the non-POJ group, though no difference was seen at 10 days (Fig. 1). It was also noted that the T.Bil concentra-

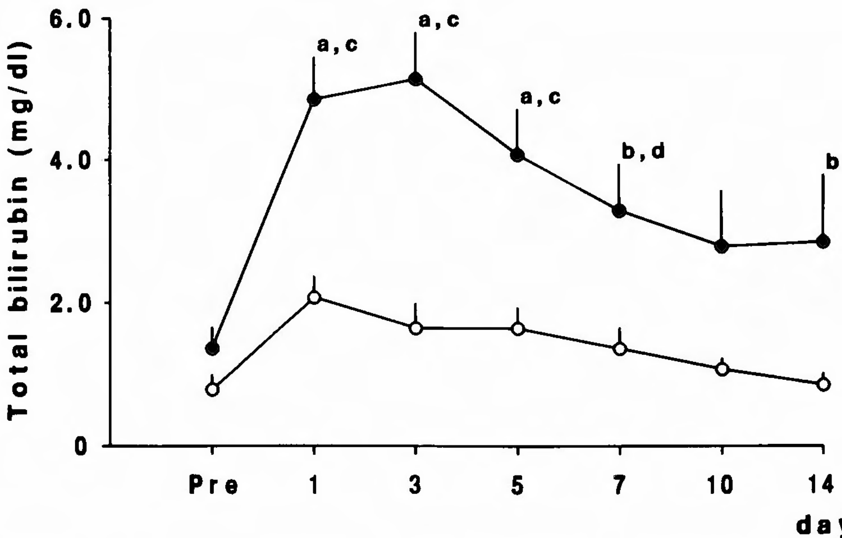

Fig. 1 Changes in total bilirubin concentration in the blood. The non-POJ (○, n=10) and POJ (●, n=14) groups were compared. Values are the means±SEM. [a] $p<0.01$ vs ○. [b] $p<0.05$ vs ○. [c] $p<0.01$ vs ● and ○ before operation. [d] $p<0.05$ vs ● and ○ before operation. Pre: the time before the operation.

tions increased absolutely during the first 7 days after the operation compared to the preoperative value, and returned to the preoperative value in the next 3 days (Fig. 1), whereas in the non-POJ group, the bilirubin concentration remained almost the same throughout the pre- and post-operative periods (Fig. 1).

The D.Bil concentration had increased significantly at 1, 3, 5 and 7 days after the operation in the POJ group when compared to the non-POJ group (Fig. 2A). In the POJ group, when compared to the preoperative value, the D.Bil concentration had increased significantly from 1 to 5 days after the operation, but it returned to the preoperative value in the next 3 days. The D.Bil concentration in the non-POJ group was unchanged throughout the pre- and post-operative periods.

The I.Bil concentration had increased significantly at 1 and 3 days after the operation in the POJ group when compared to the non-POJ group (Fig. 2B). Moreover, the bilirubin concentration had increased significantly from 1 to 5 days after the operation compared to the preoperative value, but it recovered in the next 2 days. However, in the non-POJ group, the I.Bil concentration was un changed throughout the pre- and post-operative periods.

Preoperative data related to liver function are shown in Table 3, and there was no significant difference between the parameters for the two groups. Pathologically, it was noted that the incidence of cholangitis was much higher in the POJ group than in the non-POJ group (Table 4). Blood loss was greater in the POJ group than in the non-POJ group (Table 2). No significant difference between the two groups was seen in liver functional parameters including GPT after operation (Table 5). The morbidity rate in the POJ group was higher than that in the non-POJ group, although the mortality rate was similar in the two groups (Table 6).

When the POJ group was divided into two groups according to the presence or absence of pre-

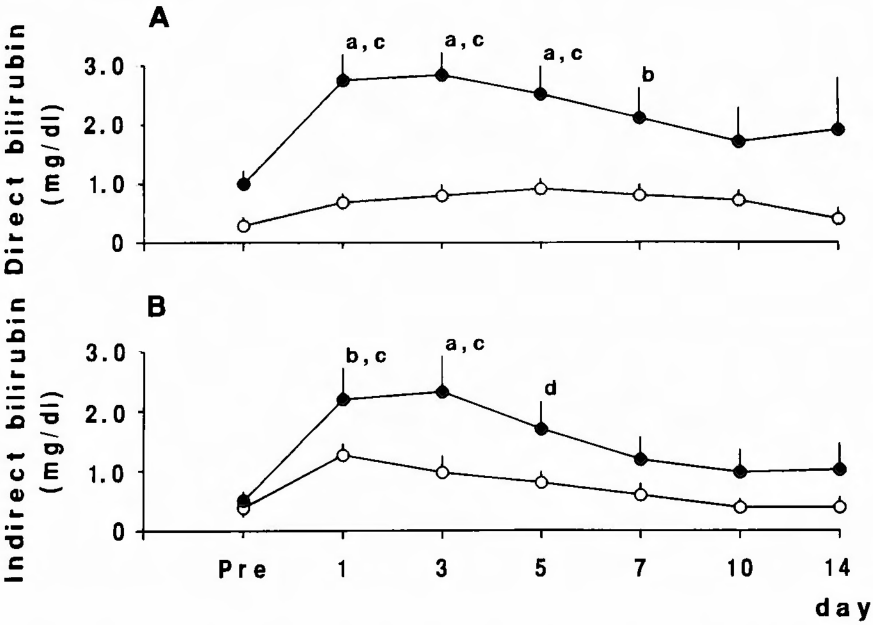

Fig. 2 Alterations in direct (A) and indirect (B) bilirubin concentrations in the blood. The non-POJ (○, n=10) and POJ (●, n=14) groups were compared. Values are the means±SEM. [a] $p<0.01$ vs ○. [b] $p<0.05$ vs ○. [c] $p<0.01$ vs ● and ○ before operation. [d] $p<0.05$ vs ● and ○ before operation. Pre: the time before the operation.

operative cholangitis and post-operative complication, there was no significant difference in the daily bilirubin concentration between the two groups in each case (Tables 7A and 7B).

Discussion

Major hepatectomy resulted in hyperbilirubinemia (Fig. 1). This is keeping with the view that a transient increase in the serum bilirubin concentration occurs after hepatic lobectomy[2–5]. Moreover, it was demonstrated that hepatectomy for biliary tract carcinoma elicited a further increase in the serum bilirubin concentration in the POJ group (Fig. 1). This could mean that postoperative bilirubin dynamics is substantially affected by preoperative disturbance of passage through the biliary tract.

Bilirubin metabolism involves the following processes: hepatic uptake of bilirubin, intracellular storage and transport of bilirubin, hepatic conjugation of bilirubin and excretion of bilirubin[20]. The increase in the bilirubin concentration after hepatectomy has therefore been attributed to an underlying dysfunction of bilirubin metabolism in one of the processes mentioned above. In preoperative data, there was, however, no sign which suggests dysfunction in one of the bilirubin metabolic processes, and it is not easy to explain the increase observed. On the other hand, biliary obstruction, which often results in cholangitis, was seen in the POJ group (Table 4). This may occur because of

Table 3 Liver functional parameters before operation in the non-POJ (I, n=10) and POJ (II, n=14) groups

	I	II
GOT (IU/l)	49 ± 13	44 ± 8
GPT (IU/l)	66 ± 20	84 ± 19
LDH (IU/l)	418 ± 40	374 ± 20
Alp (IU/l)	641 ± 184	574 ± 110
γGTP (IU/l)	361 ± 132	199 ± 42
Alb (g/dl)	4.0 ± 0.2	3.9 ± 0.1
ChE (IU/l)	6664 ± 434	5956 ± 51
PT (%)	106 ± 5	95 ± 5
HPT (%)	106 ± 11	112 ± 10
KICG	0.181 ± 0.003	0.163 ± 0.009

Values are the means±SEM.

Table 4 Liver function data before operation in the non-POJ (I, n=10) and POJ (II, n=14) groups

	I	II
OGTT		
linear	0	0
parabolic	7	13
Cholangitis		
yes	0	5[a]
no	10	9

[a] $p<0.05$ vs I.

bilirubin conjugation insufficiency due to biliary obstruction. Support for such a speculation comes from the finding that direct bilirubin response was dominant (Fig. 2); direct bilirubin response predominantly implies that in the process after bilirubin conjugation by bilirubin uridine diphosphatate glucuronyl-transferase in hepatic microsomes, hypohepatocellular function exists.

Serum bilirubin concentrations returned to normal within 2 weeks in operated patients with normal livers, but this return was retarded in operated patients with cirrhosis[21,22]. In cirrhotic patients, who were persistently abnormal with a terminal rebound by the end of the second week, the serum bilirubin concentration failed to return to normal[22]. In the present study, the increased bilirubin concentration due to the operation returned rapidly to the preoperative value in the non-POJ group, but it was persistently high at 14 days in the POJ group. This could mean that the POJ group had suffered similar hepatic damage to cirrhosis, although it should be remembered that the pathophysiology in cirrhosis involves not only bilirubin metabolism but also various elements.

Intrahepatic cholestasis resulted in an increase in serum direct bilirubin after a general operation[23]. It has also been shown that a major change in bilirubin was in the direct bilirubin immediately after hepatic lobectomy[4], but there are few reports on the bilirubin fraction after hepatectomy. In this study, the postoperative direct bilirubin concentration in the POJ group shifted to a higher level (Fig. 2). Our findings could therefore be interpreted as meaning that that hyper-direct bilirubinemia associated with major hepatectomy originated in intrahepatic cholestasis. In addition, because the direct bilirubin concentration was persistently higher at 7 days compared to the preoperative value, severe cholestasis may have existed in the POJ group.

The indirect bilirubin concentration in the POJ group also shifted to a higher level (Fig. 2). Blood transfusion induces hyperbilirubinemia due to the increased pigment load[1,8], and hemolysis of transfused red blood cells with increased production of bilirubin is a possible cause of the rise in unconjugated bilirubin[24], but there was no difference in the blood transfusion volume. Thus blood transfusion could be excluded from the observed findings, although the amount of blood loss was less in the non-POJ group than in the POJ group. Further study is necessary to clarify the increase in indirect bilirubin response.

Table 5 Liver functional parameters after operation in the non-POJ (I, n=10) and POJ (II, n=14) groups

	Days after operation					
	1	3	5	7	10	14
GOT (IU/l)						
I	384±60	127±17	70±8	54±9	68±15	44±8
II	346±78	87±14	38±3	35±7	35±4	40±5
GPT (IU/l)						
I	309±38	177±29	114±18	87±15	116±36	83±27
II	292±44	168±46	84±19	57±12	51±12	58±15
Alp (IU/l)						
I	319±55	276±42	296±42	319±43	317±41	327±55
II	301±53	260±28	271±40	311±59	351±67	382±75
γGTP (IU/l)						
I	171±55	128±38	127±26	124±22	114±20	102±18
II	95±18	74±12	77±15	84±19	89±19	89±18

Values are the means±SEM.

Although there is a correlation between the post-operative serum bilirubin concentration and the extent of the liver resected[6,7,25]. No difference was seen between the two groups in the resected liver weight to body weight ratio. The liver resection factor could therefore be excluded from the observed findings.

Similar surgical treatment could be conducted on this series of patients based on the finding that GOT and GPT which directly reflect surgical damage to liver were similar to each other. As mentioned above, intrahepatic cholestasis may be the main origin of postoperative hyperbilirubinemia, but there were no difference in Alp or γGTP indicating a marker of cholestasis in the two groups. There might be much room for the choice of a marker indicating cholestasis in this situation.

By using stepwise logistic and discriminant analyses, Nagino and his coworkers defined the risk factors for hepatic failure after hepatectomy for carcinoma of the biliary tract. They identified the linear pattern for the oral glucose tolerance test, cholangitis and indocyanine green disappearance rate as good predictors most closely related to hepatic failure[26]. In this study, cholangitis is considered to be one factor causing hyperbilirubinemia, but both the oral glucose tolerance test and indocyanine green disappearance rate failed to detect the difference. It appears that these tests are insensitive in detecting liver dysfunction which is complicated by hyperbilirubinemia.

Bacterial infection of the biliary tract and gastrointestinal bleeding are considered as factors causing prolonged jaundice[27-29]. In this study, incidence of pre-operative biliary tract infection or post-operative gastrointestinal bleeding was high in the POJ group (Tables 4 and 6), and no correlation between these components and the increased bilirubin response was obtained (Tables 7A and 7B). However, this result requires verification in larger POJ group because the POJ group examined was small.

It has recently proposed that a decrease of conjugated bilirubin is a better parameter reflecting the recovery phase of bile congestion than alkaline phosphatase, total bilirubin or direct bilirubin[30]. Monitoring conjugated bilirubin might be useful in tracing recovery from detected hepatic dysfunction. Although the exact mechanism of hyperbilirubinemia remains unclear, the knowledge of post-operative changes and patterns of bilirubin allows us to better manage patients who have had a major hepatectomy.

These findings led us to conclude that characteristic hyperbilirubinemia is developed after major hepatectomy in patients with biliary tract carcinoma, and the bilirubin response may originate in un-

Table 6 Postoperative data in the non-POJ (I, n=10) and POJ (II, n=14) groups

	I	II
Major complication		
Liver abscess	1	1
Cholangitis	1	1
Ileus	0	1
Hepaticojejunostomy leakage	0	1
Intraabdominal infection	0	5
MRSA infection	0	1
Gastrointestinal bleeding	1	2
Morbidity rate	2/10 (20%)[a]	9/14 (64%)
Mortality rate	0/10 (0%)	2/14 (14%)

[a] $p<0.05$ vs II.

Table 7A Changes in bilirubin concentration in the POJ group with cholangitis (I, n=5) and non-cholangitis (II, n=9)

	before	Days after operation					
		1	3	5	7	10	14
T.Bil (mg/dl)							
I	1.8±0.4	6.4±0.9	6.1±1.0	5.6±1.3	4.6±1.5	3.8±1.6	4.4±2.6
II	1.1±0.2	4.0±0.4	4.7±0.8	3.3±0.5	2.5±0.4	2.2±0.6	2.1±0.8
D.Bil (mg/dl)							
I	1.5±0.3	3.9±0.9	3.6±0.5	3.5±0.6	2.9±0.7	2.4±0.9	3.0±1.7
II	0.7±0.1	2.0±0.2	2.4±0.4	1.8±0.3	1.6±0.3	1.4±0.5	1.3±0.6
I.Bil (mg/dl)							
I	0.4±0.1	2.5±0.9	2.5±0.9	2.1±0.8	1.7±0.8	1.5±0.7	1.4±0.9
II	0.5±0.1	2.0±0.3	2.3±0.6	1.4±0.2	0.9±0.1	0.8±0.1	0.8±0.2

Values are the means±SEM.

Table 7B Changes in bilirubin concentration in the POJ group with complication (I, n=9) and non-complication (II, n=5)

	before	Days after operation					
		1	3	5	7	10	14
T.Bil (mg/dl)							
I	1.5±0.3	5.2±0.7	5.4±0.8	4.5±0.9	3.7±0.9	3.3±1.0	4.0±1.6
II	1.3±0.2	4.4±0.5	4.8±1.1	3.4±0.7	2.4±0.6	1.8±0.4	1.1±0.2
D.Bil (mg/dl)							
I	1.0±0.2	3.0±0.6	3.0±0.4	2.7±0.5	2.4±0.5	2.1±0.7	2.6±1.1
II	0.8±0.2	2.1±0.2	2.5±0.5	1.8±0.4	1.5±0.4	1.0±0.3	0.6±0.1
I.Bil (mg/dl)							
I	0.4±0.1	2.1±0.6	2.4±0.6	1.7±0.5	1.4±0.5	1.2±0.4	1.3±0.5
II	0.4±0.1	2.2±0.4	2.2±0.8	1.6±0.3	0.9±0.2	0.7±0.2	0.5±0.1

Values are the means±SEM.

derlying preoperative biliary passage disturbance.

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和文抄録

胆道癌に対する大量肝切除後に出現する高ビリルビン血症

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大量肝切除が行われた胆道癌24例を対象に血清ビリルビン濃度の推移を検討した．対象を術前に閉塞性黄疸を来した群（POJ 群，14例）と閉塞性黄疸を来さなかった群（non-POJ 群，10例）とに分配した．POJ 群には術前に減黄の目的で胆道ドレナージを施行した．総ビリルビン濃度は手術直前に群間差を認めなかったが，術後 1, 3, 5, 7, 14病日に POJ 群で高値を示した．直接ビリルビン濃度は術後 1, 3, 5, 7 病日，間接ビリルビン濃度は術後 1, 3 病日に POJ 群で高値となった．肝機能指標は手術直前及び術後14日間で群間差を認めなかった．胆管炎の頻度は POJ 群で高率であった．出血量と合併症は POJ 群で多く見られた．

これらの所見から，胆道癌に対する大量肝切除後には特徴的な高ビリルビン血症が発症すること，そうしたビリルビン反応は術前から併存する胆道の通過障害に由来することを推定した．